Intramolecular Oxa-Michael Reaction on α,β-unsaturated α-amino-δ-hydroxycarboxylic Acid Esters. Synthesis of functionalized 1,3-dioxanes

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A highly diastereoselective intramolecular oxa-Michael reaction on α,β-unsaturated α-amino-δ-hydroxycarboxylic acid esters is presented; 1,3-dioxanes functionalized in positions 2,4 and 6 were obtained in good yields and with excellent selectivities; an experimental and computational study was carried out to understand the reaction course in terms of yields and selectivities. The reaction proceeds under mild reaction conditions using highly electrophilic aldehydes and ketones.

Introduction

Since the first published work on tandem nucleophilic addition-intramolecular oxa-Michael reaction by Evans and Prunet,[1] this process has emerged as a very powerful tool to synthesize *syn* 1,3-diols. The evidence lies on the significant number of papers where the reaction is used in total synthesis of natural products.[2] Besides there is also an important number of methodological studies trying to generalize the reaction to a significant number of Michael acceptors.[3] As part of our research program, we have been interested in the application of that addition/oxa-Michael sequence to the diastereoselective synthesis of 1-amino-2,4-diols. This motif is present in some interesting molecules, because of its biological properties and structures (Figure 1); in consequence, straightforward methods to synthesize this fragment are particularly desirable. Traditionally, the 1-amino-2,4-diols have been synthesized by long reaction sequences where the three stereocenters are created by independent steps,[4] thus making the addition/oxa-Michael sequence applied to the correctly functionalized substrates an interesting alternative to synthesize the previously mentioned functionalized diols; nonetheless, there is only one example in literature for the application of this sequence to a Michael acceptor substituted in α position to the electron withdrawing group by a nitrogen[5] and very few examples where the substitution is with an oxygen in the same position.[3b, 5]

We can speculate about the reasons for the almost absence of information in this field; taking an α,β-unsaturated α-amino ester as an example, the analysis of its structure shows a double reactivity of the β carbon to the carbonyl group, in fact it can react as a nucleophile or as an electrophile, hence making difficult the use of these systems as Michael acceptors.

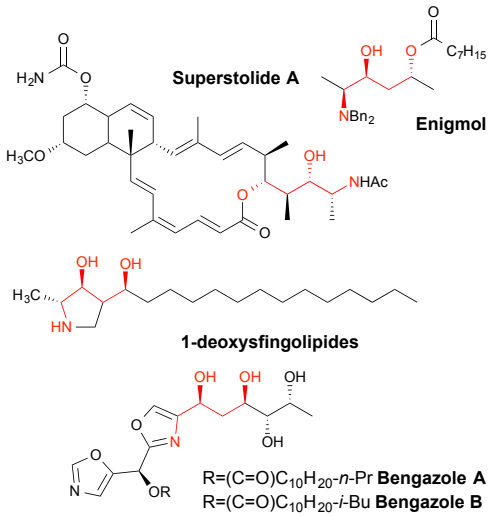


Figure 1. Some bioactive compounds containing the 1-amino-2,4-diol motif.

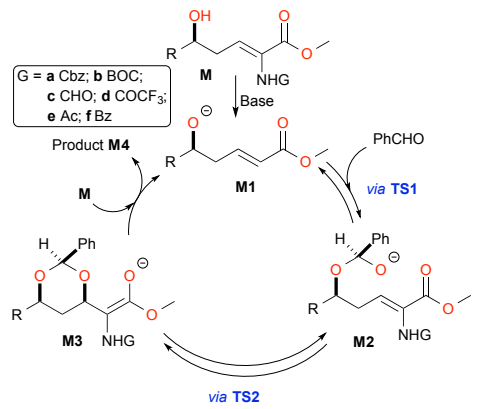
The proposed reaction mechanism is shown in Scheme 1; the homoallylic alcohol **M** is deprotonated by the base generating **M1**, then the addition of the alkoxide to the electrophilic reagent takes place to produce the intermediate **M2** (*via* a transition state **TS1**), which can react by an intramolecular Michael addition *via* a second transition state **TS2**, forming the enolate **M3**, which is basic enough to deprotonate another molecule of the substrate **M** generating **M4**. Up to date there are no additional mechanistic studies and the question for the reactivity of α-hetero-substituted substrates remained unsolved from a practical and mechanistic point of view.

Motivated by this lack of information and by the possibility to apply this transformation to the synthesis of some more complex systems like those presented before, we report herein a computational and experimental study on addition/ intramolecular oxa-Michael sequence using α,β-unsaturated α-amino-δ-hydroxycarboxylic esters and several carbonyl compounds as substrates.

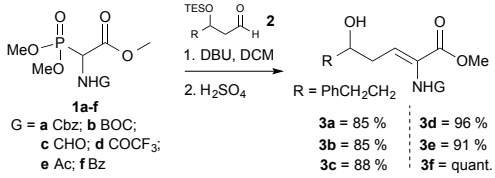
Results and Discussion

The synthesis of the starting material was carried out by a Horner-Wadswoth-Emmons (HWE) reaction using

phosphonates derived from glycine **1** and β-hydroxy aldehydes **2**. Two carbamates are commercially available (Cbz protected **1a** and Boc protected **1b**), and the replacement of the carbamate group by an acyl group was carried out according with the previously described procedures.[6] With the phosphonates **1** in hand we established the best conditions for the HWE reaction, inspired by the work published by Marsden in 2005.[7] Aldehyde **2** was obtained as previously described in literature,[8] starting from hydrocinnamaldehyde. In all cases the desired alcohols **3** were obtained with excellent yields (see Scheme 2); the group on the nitrogen atom has no apparent influence on the reaction yield, besides in all cases only one diasteromer was observed in the ^{1}H NMR spectra of the crude reaction mixtures.

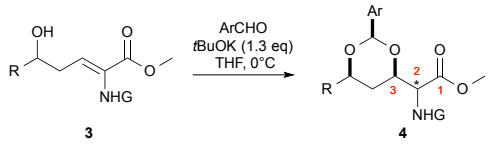


Scheme 1 Reaction Mechanism.



Scheme 2 HWE reaction to obtain α,β-unsaturated α-amino-δ-hidroxycarboxylic acid esters.

Table 1 Preliminar experiments for the addition/oxa-Michael sequence.



Entry	G	Ar (equiv.)[a]	Yield	2,3-*syn*:*anti* [b]
1	CH_3CO	*p*-MeOPhCHO (5)	-	-
2	CH_3CO	PhCHO (5)	9 %	d.r 70:30
3	CHO	*p*-NO_2PhCHO (3.3)	36%	d.r 63:37

[a]The reaction was performed making successive additions of the base and the aldehyde each 15 min. [b]Determined by ^{1}H NMR of crude product.

During the optimization process, and following the observations of Marsden et. al. we used other bases like *t*BuOK and tetramethylguanidine, however, even if the product was obtained, the DBU exhibited always better results.

Having obtained the starting materials, we began our study with the reaction of **3** with several aldehydes. The typical reaction conditions described by Evans and Prunet[1] and used almost unchanged in all the reports afterwards, include the use of substoichiometric quantities of base and 3 to 4 equivalents of benzaldehyde, but in our case all the attempts using those conditions were unsuccessful, leading only to recovered starting material. It has to be noted that the amide or carbamate protons in **3** are more acidic than the alcohol according to the pKa reported by Bordwell and coworkers.[9] Having that information in mind, one extra equivalent of base was used in order to completely deprotonate the nitrogen before the alcohol (Table 1). While the reaction between **3e** and *p*-methoxybenzaldehyde (PMB) was ineffective and the starting material was recovered unchanged even after 36 h (entry 1), the reaction with the more electrophilic benzaldehyde, [10] led to the desired product but only with 9% yield (entry 2). The conversion could not be improved neither by increasing the reaction time nor the temperature. As mentioned before the reactivity of carbon 3 in the substrate may exhibit a double reactivity, it can react as an electrophile or as a nucleophile and literature shows examples in both ways. In 2000 Maia et. al[11] described the addition of nitrogen and sulfur nucleophiles to α,β-dehydroamino esters as Michael acceptors; on the other hand, Palacios and coworkers[12] reported the reaction of similar structures as nucleophiles, thus reacting with aldehydes as enamines in an aldol type condensation. Nevertheless, in our case the product of an aldol type reaction was never observed. This motivated us to use an even more electrophilic aldehyde; fortunately, the reaction with *p*-nitrobenzaldehyde (PNB) worked and the desired product was isolated in 36% yield and as a mixture of two diastereomers.

Some starting material **3c** was recovered along with *p*-nitrobenzyl alcohol. The later was presumably formed by Cannizzaro reaction of the aldehyde, explaining the low yield and suggesting the need of a larger excess of aldehyde.

It has to be highlighted that in this process three stereogenic centres are generated in a single step. However, the products were observed as mixtures of two diastereomers. The stereochemistry was assigned after a careful analysis of ^{1}H NMR coupling constants, particularly those between protons on carbons 2 and 3; the selectivity for the dioxane ring was complete and the two isomers (2,3-*syn*/*anti*) are formed in the last protonation step. A detailed discussion about the mechanism will be presented later in this manuscript.

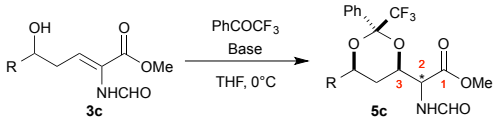
The results shown in table 1 prompted us to optimise the reaction conditions and to use other electrophilic reagents. We have recently reported the use of trifluoroacetophenone (TFAP) in addition/oxa-Michael sequences[5] using simple substrates, so we decided to use this ketone as the electrophile in the optimisation process. Table 2 shows the results obtained in this field.

Entries 1 and 2 show some very interesting results. First the yield in entry 1 compared with those described in table 1 is much better; on the other hand, changing the counter-ion to Li^+ the selectivity is significantly improved even if the yield is lower. Increasing the

reaction time has no significant influence on the reaction yield but the selectivity drops slightly (entry 3). Changing the base to LiHMDS provides good yields and selectivities (entry 4); again increasing the reaction time has a deleterious effect on selectivity, even if the yield is slightly better (entry 5). Entries 6 and 7 were performed using a smaller excess of ketone and a reduced quantity of base; in both cases yields were comparable to those described before and the effect of longer reaction times was also observed. Entry 8 shows an experiment performed with one single addition of the reagents providing excellent selectivity but low yield. The conditions of entry 6 were used in the following experiments.

The stereochemistry of the major diastereomers was determined by ^{1}H NMR analysis and confirmed by X-ray crystallographic analysis of compound **5c** as previously reported.[5]

Table 2 Optimization of reaction conditions.



Entry	$PhCOCF_3$ (equiv)	Base (equiv)	Time (h)	Yield %[d] (2,3-*syn*:*anti*)[e]
1	3.3	*t*BuOK (3.3)	4.5	85[a] (82:18)
2	5	*t*BuOLi (1.3)	3	37[b] (93:7)
3	5	*t*BuOLi (1.3)	12	36[b] (90:10)
4	6	LiHMDS (1.4)	3	74[b] (91:9)
5	6	LiHMDS (1.4)	12	78[b] (77:23)
6	**5**	**LiHMDS (1.3)**	**3**	**79[b] (89:11)**
7	5	LiHMDS (1.3)	6	71[b] (78:22)
8	3	LiHMDS (1.1)	3	52[c] (93:7)

[a]Three addition of 1.1 equivalents of base and ketone were made. [b]The starting material was treated with 1.1 equivalent of base and 3 equivalents of ketone, then consecutive additions of 0.1 equivalents of base and 1 equivalent of ketone were made. [c]The reaction was performed making one addition of 1.1 equivalents of base and 3 equivalents of ketone. [d]For isolated products. [e]Determined by ^{1}H NMR of crude product.

We then applied the optimised conditions to other substrates with PNB and TFAP as shown in tables 3 and 4 respectively. We started using PNB as the carbonyl compound and the α,β-unsaturated α-amino-δ-hydroxycarboxylic esters were protected on the nitrogen with carbamates, as these are common protecting groups for amines. Applying the conditions described before, the reaction never went to completion, the yields were poor, but the starting material could be recovered. Use of a larger excess of aldehyde or longer reaction time did not improve the yields (products **4a** and **4b**), so apparently a carbamate group is not a desirable substituent for this transformation. Then we turned our attention to amides, which worked much better than carbamates; specifically, electron-donating groups as substituents of the amide moiety exhibited better results, but using the strong electron-withdrawing group CF_3 caused a dramatic fall in yield and selectivity (compare compounds **4c** to **4d**). As mentioned before, the nitrogen has to be completely deprotonated before the alcohol; therefore, a formal negative charge on the nitrogen atom increases the enamine character of the carbon in β position to the carbonyl group (more nucleophilic). Thus, when the strong electron-withdrawing group is present, the negative charge on the nitrogen is stabilized and the β carbon has more electrophilic character; in consequence we expected better yields with this substituent, which is not the case. We observed a complex mixture of products during this experiment, showing the high reactivity of the substrate; unfortunately, all our efforts to increase the yield were unsuccessful. The selectivities in all cases are comparable and the reaction showed some preference for the 2,3-*syn* products.

Table 3 Scope using *p*-nitrobenzaldehyde.

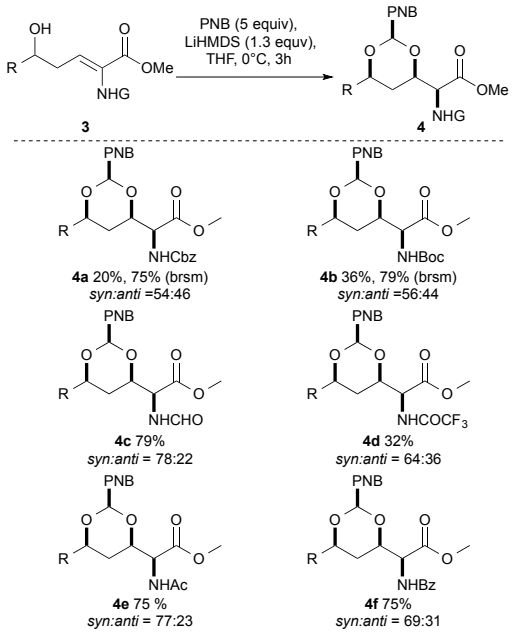
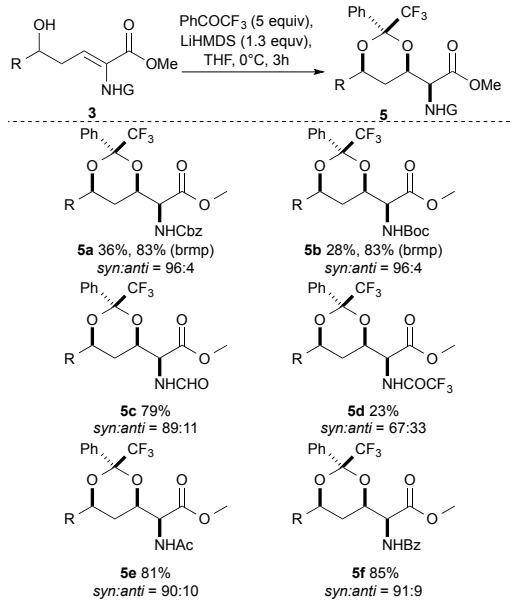
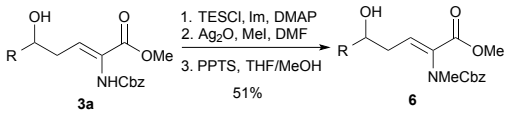


Table 4 Scope using trifluoroacetophenone.

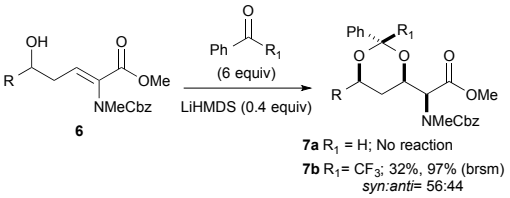


The use of TFAP is shown in Table 4. In these cases, the yields showed the same behavior observed with PNB: low yields are obtained with carbamates, but the starting material can be recovered (products **5a** and **5b**); with strong electron withdrawing amides (product **5d**) yield is also low and selectivity is much lower than with carbamates, however, better yields are obtained with regular amides and there is no significant difference between them (see products **5c**, **5e** and **5f**). On the other hand, the 2,3-*syn*/*anti* selectivities in all cases were much higher compared with those observed with PNB, thus suggesting that the enolate conformation, before protonation, is clearly different when using PNB or TFPA. The selectivity of product **5d** compared with the other amides suggests that there is no steric influence on the protonation step, but the difference should be related to electronic effects.

All the results showed in Tables 3 and 4 demonstrate that the addition/oxa-Michael sequence is useful to synthesise the motif we aimed for; however, it is more desirable to use TFAP than substituted benzaldehydes. To the best of our knowledge this is the first report about the use of PNB as the electrophilic reagent in the sequence described by Evans and Prunet. The use of highly electrophilic aldehydes or ketones clearly increases the reactivity, providing a useful alternative when less reactive Michael acceptors are used. Our results also showed that the chemical behaviour of α,β-unsaturated α-amino-δ-hydroxycarboxylic esters under the conditions explored in this study is exclusively as Michael acceptor and they do not react as nucleophiles. Hence, we explored one additional variation in their structure.



Scheme 3. Synthesis of substrate **6** without and acidic proton on the nitrogen.



Scheme 4. Addition/oxa-Michael sequence with **6**.

In all the cases described above, the nitrogen atom is completely deprotonated before the alcohol, and as it was already mentioned the product of an aldol type reaction was never observed; however, we were curious about the use of substrates without an acidic proton on the nitrogen atom. Fortunately, compound **3a** was easily protected as a triethylsilyl ether using classical conditions, then N-alkylation using Ag_2O as the catalyst followed by cleavage of the silyl ether led to compound **6** in good overall yield as showed in Scheme 3.

With this product in hand we tried the reaction with benzaldehyde instead of PNB, however the reaction did not start and the starting material was recovered unchanged. When we used TFPA, the product **7b** was obtained in poor yield and as a mixture of diastereomers (56:44) (see Scheme 4). This result showed once again that carbamates are the less reactive substrates and they may be not suitable substrates for this reaction. On the other hand, avoiding the acidic proton does not have a positive influence on the substrate reactivity.

After that, we carried out a complementary computational DFT study mapping the reaction profile **M1** → **M3** according to Scheme 1, using three model systems (Figure 2) in order to examine the influence of the substituents in both reagents over the reaction course, the influence of different counter-ions (Li^+ or K^+), and the rationale for the stereochemical outcome. The tables reporting the complete results are presented in the Supporting Information.

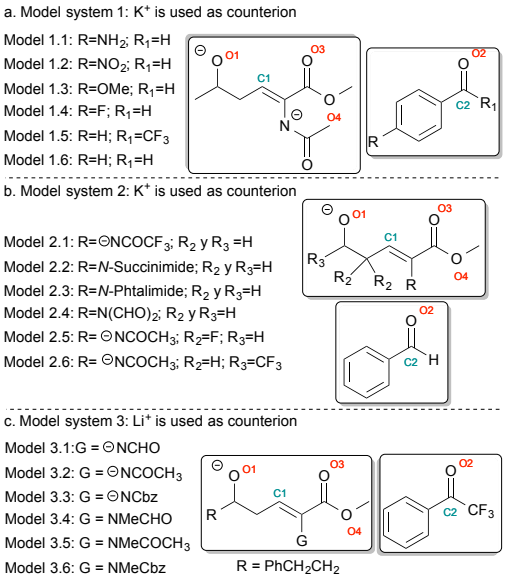
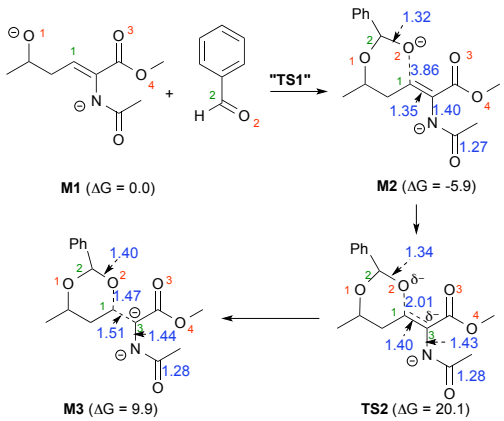


Figure 2. Model systems 1, 2 and 3.



Scheme 5. Model system 1.6: relative Gibbs energy (kcal/mol) and geometry parameters (in Angstroms) of the various critical points localized on the potential energy surface

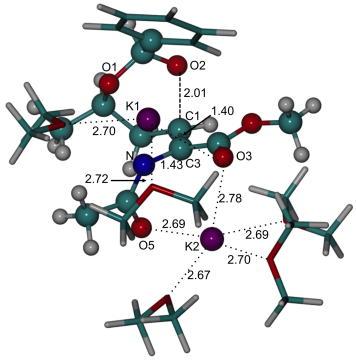


Figure 3. 3D representation of TS2 (model 1.6): two K^+ and five dimethyl ether molecules are included. Bond lengths are in Angstroms

The reaction is carried out in THF, a solvent with a quite low dielectric constant (ε = 7.6) and it is therefore plausible to believe that the metal counter-ions interact closely with the negatively charged reacting species, instead of being dispersed in the bulk. Thus, with the purpose of better reproducing the experimental conditions, and depending on the negative charge of the reacting species, we included one or two metal counter-ions in the calculations. Additionally, to explicitly simulate the presence of solvent, the model systems also include a proper number of dimethyl ether molecules to saturate the metal ions.

We initially present the results of the calculations (Scheme 5 and Table S-1), aimed at analysing the effect of R and R_1 and determining the general reaction mechanism. For this purpose, we used model system 1, represented in figure 2a.

The calculations showed a two-step mechanism, in which the initial attack of the nucleophile O1 to the carbonyl C2 affords the doubly charged, stable intermediate **M2**.

In spite of our efforts and due to the alkoxide high reactivity, we could not locate the **TS1** transition state, which must be associated to a very low energy barrier. The next step is the nucleophilic addition of O2 to C1, delivering the **M3** adduct. This intramolecular cyclisation is the rate-determining step of the process and thus any influence of the substituents on the carbonyl compound must result in a different stability of **TS2** (see Figure 3). As expected, the addition of the alkoxide to the carbonyl compound is an exergonic process and it is directly related to the electrophilicity of the reagent, which means the more electrophilic the carbonyl compound (more electron-withdrawing character of R and R_1), the more energy will be released when the addition takes place. The electronic effect of R and/or R_1 on the **M2** → **M3** energy barrier might look puzzling, although our computational results, which agree with the experimental evidences, showed a clear pattern: as the electron withdrawing character of R and/or R_1 increases, the energy of **TS2** drops. Therefore, the stabilising effect of strong EWGs on the negative charge on O2 in **TS2** must be more important than the reduced O2 nucleophilicity caused by the same groups. It is evident that the prevalence of the former effect determines stabilisation of the whole energy profile and in particular of **TS2**, favouring the reaction. As a matter of fact, as the system passes **TS2** and reaches the carbanionic species **M3**, substrate molecules containing a protonated O1 still present in the medium transfer a proton to the negative C1 very rapidly and irreversibly. The protonation process is clearly an acid-base reaction, the equilibrium of which is definitely shifted towards the product. Therefore, under the experimental conditions, the lower is the **M2** → **M3** energy barrier, the higher is the number of molecules converting to the final products. That means, with strongly electrophilic reagents like PNB or TFAP the energy barrier is lower and the reaction should proceed easier than with less electrophilic aldehydes like benzaldehyde or PMB, as observed experimentally.

With the purpose of examining in detail the electrophilic system features in the second step, we evaluated the potential energy surface using model system 2 (Figure 2b) consisting of one benzaldehyde molecule and several dehydro amino esters bearing different EWG or lacking any proton on the nitrogen atom. In any of those cases, the electrophilic character of the Michael system should be enhanced. The results of the computations (summarised in Table S-2) revealed that the relative stability of the transition state **TS2**, and the relative activation energy slightly change comparing with model system 1, which features no EWG on the Michael acceptor (Table S-1 vs. Table S-2).

These data, in agreement with the experimental results, also indicate that extra EWGs on the Michael system are not as efficient as expected in stabilising the formal negative charge on the nitrogen and consequently they do not significantly decrease the nucleophilic or enamine character of C1. Conversely, the use of substrates containing a doubly substituted nitrogen atom (models 2.2 to 2.4) dramatically decreases the most important intrinsic activation energy (difference between **TS2** and **M2**). Thus, the absence of a negative charge on the nitrogen atom appears to be crucial for increasing the electrophilicity of C1 and allowing the reaction with less electrophilic carbonyl compounds such as benzaldehyde.

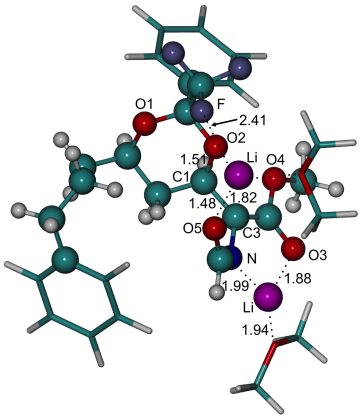


Figure 4. 3D representation of **M3** (model 3.1). Bond lengths are in Angstroms

Finally, an analysis of the **M3** intermediate in model system 3 (Figure 2c and Table S-3), which comprises a TFAP molecule reacting with α,β-unsaturated α-amino-δ-hydroxycarboxylic esters and Li^+ (instead of K^+) as counter-ion, can rationalise the higher selectivity experimentally observed with this metal and the higher amount of the final 2,3-*anti* stereoisomer if the reaction is carried out over a longer time (see Table 2, entries 3 to 6). Importantly, given the initial alkene stereochemistry, the **M3** structure (Figure 4) is such

that the two successive protonation events would eventually lead to the final product in the 2,3-*syn* configuration only.

In fact, the first of those protonations, on C3, which delivers the final product **M4**, can occur on one prochiral face only due to the complex network of coordination bonds, which involves the positive counter-ions and hinders the other face. The protonation of the other prochiral face is possible only after a rotation about the C1-C3 bond. The complexity of this torsion prevented us to determine the associated transition state, but it is plausible that, under the experimental conditions (0°C), it must be difficult, as it means disrupting the above-mentioned strong and intricate coordination structure. Thus, as **M3** forms, all the substrate molecules containing a protonated O1 still present in the medium, protonate it, producing **M4_syn** (Figure 5), which, after quenching the reaction, leads to the final 2,3-*syn* product.

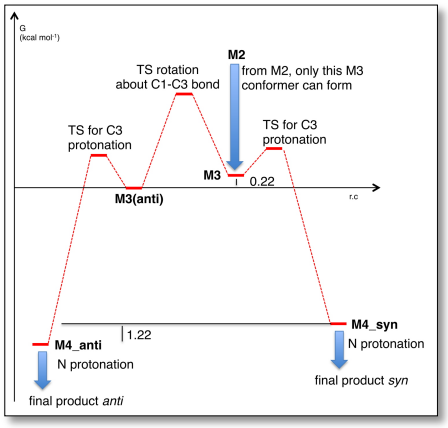


Figure 5. Energy profile for the system evolution from **M3** with model 3.1.

This protonation is very likely to be irreversible and faster than the rotation. When the available protons in the medium run out, the conversion of **M3** to **M4_syn** is no longer possible and the above-mentioned rotation slowly begins to occur producing a conformer, **M3(anti)**, which eventually leads to the 2,3-*anti* product. In other words, an equilibrium between **M3** and **M3(anti)** establishes in which both species are almost equally populated, being the Gibbs free energy difference between them 0.22 kcal mol^{-1} only. Thus, if the reaction is quenched prior to reaching this equilibrium, i.e. when the amount of **M3(anti)** is increasing, more **M4_anti** is produced and the amount of the final 2,3-*anti* isomer over the 2,3-*syn* rises, as the reaction proceeds. If, on the other hand, the acid is added after the equilibrium has been reached, i.e. when the amounts of **M3** and **M3(anti)** are constant over time, the *syn*:*anti* ratio of the products is also constant, even at longer reaction time. This scenario is in agreement with the experimental outcome (Table 2, entries 3 vs. 4 and 5 vs. 6).

Model system 3 also allowed us to gain insights on the reasons of the different stereochemical outcome, when different counter-ions (K^+ and Li^+) were used. When TFAP is employed (Table S-3), the calculations show that the CF_3 group interacts with one of the cations, strengthening the above-mentioned coordination network, making the rotation even more difficult and consequently decreasing the amount of the 2,3-*anti* product obtained. This scenario is favoured when using the more coordinating Li^+ instead of K^+: the distance between the metal and the closest F atom of the CF_3 group in **M3** (model system 3.1) is 2.41 Å with Li^+ (Figure 4) and 2.96 Å with K^+. Actually, the calculations carried out on model system 3.1 with both metals revealed that, when Li^+ is employed, the most important intrinsic activation energy (difference between **TS2** and **M2**) is lower. This is probably due to a shorter distance of the forming bond (O2-C1) in **M2** with Li^+ (3.04 Å) than with K^+ (3.28 Å), which makes the successive attack easier. This is in agreement with the more coordinating character of the Li^+ cation.

Conclusions

In conclusion, we reported herein a complete study of the addition/oxa-Michael sequence on α,β-unsaturated α-amino-δ-hidroxycarboxylic acid esters. The investigation was supported by computational calculations and we showed that these substrates are suitable for the reaction sequence when strong electrophilic carbonyl compounds are used as reagents; besides, the insertion of electron-withdrawing groups on the substrate has no significant influence. Also, there is an important counter-ion effect on the selectivity of the final protonation. The mixture of computational and experimental studies serves as a prediction tool to find the best couple of reagents for this reaction.

Experimental section

General information. NMR spectra were recorded on a 400 MHz spectrometer, and the data are expressed in parts per million (ppm) referenced to TMS and trifluoracetic acid (^{19}F). Data are reported as follows: δ, chemical shift; multiplicity (recorded as br, broad; s, singlet; d, doublet; t, triplet; q, quadruplet and m, multiplet); coupling constants (J in Hertz, Hz); and integration. The chemical shifts for 13C spectra (101 MHz) are expressed in parts per million (ppm), referenced to TMS. Infrared spectra (IR) are reported in terms of absorption frequency (n, cm-1) using KBr. High Resolution Mass Spectra (HRMS) were obtained on a Q-TOF LC/MS.

Computational Details. The DFT computations were carried out using the software Gaussian 09 series.[13] The M06-2X functional proposed by Truhlar and Zhao was used in all computations.[14] All the atoms were treated with 6-31+G(d) basis set. The geometries of the various critical points on the potential surface were fully optimized with the gradient method available in Gaussian 09 including the solvent effect (PCM calculations[15]) to simulate the experimental conditions (solvent emulated was the tetrahydrofuran, used experimentally, e = 7.4257). Furthermore, with the purpose of evaluating the nature of all critical points, we computed harmonic vibrational frequencies for all of them. Geometry parameters refer to PCM optimized structures and energies values are Gibbs energies obtained with PCM frequency calculations. In order to explore more carefully the potential energy surface and the conformational space of each structure, we also performed simulated annealing calculations using the PM7[16] method available in MOPAC.[17] We used the following protocol: 1. minimization, 2. heating from 0 to 450 K in 15 ps, 3. equilibration in 10 ps, 4. exploration between 25 and 30 ps depending on the size of

the system, 5. cooling in 30 ps in all cases, 6. Minimization. In each process, the time step was 0.5 fs.

General procedure for conjugate intramolecular addition reaction. To a solution of homoallylic alcohol (1 equiv) in THF (0.1 M) at 0°C was added trifluoroacetophenone or p-nitrobenzaldehyde (3 equiv) followed by LiHMDS (1.1 equiv) and the resulting mixture was stirred for 15 min at 0°C. A second portion of trifluoroacetophenone (1 equiv) and LiHMDS (0.1 equiv) was added, after 15 min a third portion of trifluoroacetophenone (1.1 equiv) and LiHMDS (0.1 equiv) was made. The resulting mixture was then stirred at 0°C for 4 h and quenched with a saturated aqueous NH_4Cl solution. The aqueous phase was extracted 3 times with AcOEt and the combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was then purified by column chromatography. Representative examples are described below.

Methyl (*R)-2-(((benzyloxy)carbonyl)amino)-2-((2*S**,4*S**,6*S**)-2-(4-nitrophenyl)-6-phenethyl-1,3-dioxan-4-yl)acetate (4a)**. The typical procedure for conjugate intramolecular addition reaction was applied to homoallylic alcohol **3a** (0.21 mmol, 80 mg). The crude residue (*syn:anti* 54:46) was then purified by column chromatography using petroleum ether/Et_2O (8:2) to give the product **4a** as a yellow oil (22 mg, 20%). The presence of two isomers was observed in the NMR spectra, in a [0.60 (M):0.40 (m)] ratio. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.19 – 8.22 (m, 2H), 7.55 – 7.61 (m, 2H), 7.13 – 7.43 (m, 10H), 5.50 – 5.65 (m, 1.8H), 5.11 – 5.12 (m 2H), 4.51 (dd, *J* = 9.1, 2.1 Hz, 0.6H), 4.46 (dt, *J* = 11.2, 2.1 Hz, 0.6H), 3.83 – 3.91 (m, 1H), 3.79 (M) (s, 1.8H), 3.78 (m) (s, 1.2H), 2.60 – 2.96 (m, 2H), 1.80 - 2.11 (m, 2H), 1.61 – 1.71 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 170.3 (M), 169.5 (m), 156.6, 148.1, 144.3, 141.2, 135.9, 130.4, 128.5, 128.5, 128.4, 128.3, 128.3, 128.2, 128.1, 127.1, 127.0, 126.0, 123.4, 99.1 (m), 98.8 (M), 77.6 (m), 77.2 (M), 75.9 (m), 76.6 (M), 67.3 (M), 67.3 (m), 57.4 (m), 57.3 (M), 52.8 (M), 52.6 (m), 37.0, 32.7 (m), 32.4 (M), 31.1; IR: 2954, 2858, 1722, 1604, 1596, 1454, 1437, 1340, 1212, 1123, 1054, 1028, 858, 748, 698; HRMS: Calculated for $C_{29}H_{30}N_2O_8Na$ (M+Na+): 557.1900; found: 557.1886.

Methyl (*R)-2-((tert-butoxycarbonyl)amino)-2-((2*S**,4*S**,6*S**)-2-(4-nitrophenyl)-6-phenethyl-1,3-dioxan-4-yl)acetate (4b)** The general procedure for conjugate intramolecular addition reaction was applied to homoallylic alcohol **3b** (0.28 mmol, 100 mg). The crude residue (*syn:anti* 56:44) was then purified by column chromatography using pentane/AcOEt (9:1) to give the product **4b** as a colorless solid (50 mg, 36%). Mp: 110 °C The presence of two isomers was observed in the NMR spectra, in a [0.60 (M):0.40 (m)] ratio ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.22 (d, *J* = 8.6 Hz, 2H), 7.57- 7.60 (m, 2H), 7.15 – 7.35 (m, 5H), 5.56 (M) (s, 0.6H), 5.55 (m) (s, 0.4H), 5.37 – 7.42 (m) (m, 0.4H), 5.24 – 5.33 (M) (m, 0.6H), 4.44 – 4.46 (m, 1H), 3.74 – 3.94 (m, 1H), 3.79 (M) (s, 1.8H), 3.78 (m) (s, 1.2H), 2.61 – 2.98 (m, 2H), 2.10 – 1.76 – 2.10 (m, 4H), 1.45 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 170.7 (M), 169.9 (m), 155.9, 148.1, 144.5, 144.4, 141.3, 130.4, 128.5, 128.4, 127.1, 127.0, 126.0, 124.3, 123.3, 99.0 (m), 98.8 (M), 80.3, 75.9 (m), 75.7 (M), 56.8, 52.6 (M), 52.4 (m), 37.1 (M), 37.0 (m), 32.7 (m), 32.4 (M), 31.1 (M), 31.1 (m), 29.6, 28.2; IR: 1743, 1653, 1525, 1340, 1128, 1035, 858; HRMS: Calculated for $C_{26}H_{32}N_2O_8Na$ (M+Na+): 523.2056 found: 523.2060

Methyl 2-(((benzyloxy)carbonyl)amino)-2-((2*S,4*R**,6*R**)-6-phenethyl-2-phenyl-2-(trifluoromethyl)-1,3-dioxan-4-yl)acetate (5a).** The general procedure for conjugate intramolecular addition reaction was applied to homoallylic alcohol **3a** (0.21 mmol, 80 mg). The crude residue (*syn:anti* 96:4) was then purified by column chromatography using Et_2O/Petroleum ether (9:1) to give the product **5a** which was isolated as a single diastereoisomer and as a white solid (42 mg, 36%, 83% brsm). Mp: 102 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.16 – 7.47 (m, 15H), 5.60 (d, *J* = 9.9 Hz, 1H), 5.18 (m, 2H), 4.46 (dd, *J* = 9.9, 2.0 Hz, 1H), 4.41 (dt, *J* = 11.7, 2.1 Hz, 1H), 3.88 (s, 3H), 3.84 (m, 1H), 2.84 – 2.99 (m, 1H), 2.69 – 2.79 (m, 1H), 1.96 – 2.13 (m, 2H), 1.78 – 1.90 (m, 1H), 1.37 – 1.54 (m, 1H); *13*C NMR (101 MHz, $CDCl_3$) δ (ppm): 170.0, 156.7, 141.1, 136.0, 131.4, 130.0, 128.7, 128.6, 128.5, 128.3, 128.3, 128.1, 126.0, 121.2 (q, JC-F = 284.5 Hz), 98.5 (q, JC-F = 32.3 Hz), 71.0, 69.9, 67.4, 57.2, 52.6, 37.0, 31.9, 30.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -85.34; IR: 2929, 2851, 1727, 1509, 1452, 1325, 1193, 1123, 1058, 986, 725, 698; HRMS: Calculated for $C_{30}H_{30}F_3NO_6Na$ (M+Na+): 580.1923; Found: 580.1930.

Methyl (*R)-2-((tert-butoxycarbonyl)amino)-2-((2*S**,4*S**,6*S**)-6-phenethyl-2-phenyl-2-(trifluoromethyl)-1,3-dioxan-4-yl)acetate (5b).** The typical procedure for conjugate intramolecular addition reaction was applied to homoallylic alcohol **3b** (0.28 mmol, 100 mg). The crude residue (*syn:anti* 96:4) was then purified by column chromatography using pentane/AcOEt (9:1) to give the product **5b** which was isolated as a single diastereoisomer and as a pale yellow oil (44 mg, 28 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.09 – 7.57 (m, 10H), 5.33 (d, *J* = 9.2 Hz, 1H), 4.39 (d, *J* = 10.0 Hz, 2H), 3.87 (s, 3H), 3.75 – 3.89 (m, 1H), 2.86 – 2.99 (m, 1H), 2.61 – 2.83 (m, 1H), 1.74 - 2.15 (m, 4H), 1.48 (s, 9H).^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):170.3, 156.1, 141.2, 131.4, 129.9, 128.7, 128.5, 128.4, 128.4, 128.2, 126.0, 121.2 (q, $J_{C\text{-}F}$ = 284 Hz), 98.4 (q, $J_{C\text{-}F}$ = 32.2 Hz), 80.4, 71.0, 69.9, 56.6, 52.4, 37.0, 32.4, 30.9, 28.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -85.45; IR: 2930, 1750, 1718, 1497, 1452, 1367, 1193, 1123, 1059, 986, 724, 699; HRMS: Calculated: $C_{27}H_{32}F_3NO_6$ Na: 546,2079, Found: 546,2079.

Methyl (*Z*)-2-(((benzyloxy)carbonyl)(methyl)amino)-5-hydroxy-7-phenylhept-2-enoate (6). To a solution of methyl (*Z*)-2-(((benzyloxy)carbonyl)amino)-5-hydroxy-7-phenylhept-2-enoate **3a** (0.39 mmol, 150 mg), imidazole (1.2 mmol, 80 mg), DMAP (0.03 mmol, 10 mg) and dry DMF (1.3 mL) was added chlorotriethylsilane (0.59 mmol, 0.10 mL) to 0°C. The reaction mixture was stirred for 2 h and heated to room temperature overnight. The reaction mixture was quenched with MeOH. Water was added and the aqueous phase was extracted three times with CH_2Cl_2. The organic phase was washed with brine, dried with anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was dissolved in dry DMF (1 mL) with Ag_2O (1.2 mmol, 268 mg) and CH_3I (1.7 mmol, 0.10 mL) at 0°C. The mixture reaction was stirred overnight to room temperature. The solution was transferred to separatory funnel and water with AcOEt were added. The aqueous layer was extracted with AcOEt (3 x 10 mL) and organic layers were washed with brine, dried with $MgSO_4$ and concentrated under vacuum. The crude protected alcohol was dissolved in MeOH/THF (4:1) and a catalytic amount of pyridinium *p*-toluenesulfonate (0.04 mmol, 11 mg) was added and after stirring overnight the reaction mixture was

quenched with saturated aqueous $NaHCO_3$. Water was added and the product was extracted with AcOEt, washed with brine and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography using petroleum ether/AcOEt (7:3) to afford the product **6** as a pale yellow oil (79 mg, 51%). The presence of two rotamers was observed in NMR spectra in a [0.63 (M): 0.37 (m)] ratio. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.12 – 7.44 (m, 10H), 6.98 (m) (t, *J* = 7.7 Hz, 0.37 H), 6.85 (M) (t, *J* = 7.7 Hz, 0.63 H), 5.19 (m) (d, *J* = 1.4 Hz, 0.74H), 5.06 (M) (s, 1.26H), 3.67 – 3.85 (m, 1H), 3.77 (m) (s, 1.1H), 3.64 (M) (s, 1.9H), 3.05 (m) (s, 1.1H), 3.03 (M) (s, 1.9H), 2.55 – 2.86 (m, 2H), 2.31 – 2.37 (m, 2H), 1.70 – 1.85 (m, 2H), 1.61 (bs, 1H); ^{13}C NMR (δ, ppm) $CDCl_3$, 101 MHz. 164.5 (M), 164.0 (m), 156.2 (m), 155.6 (M), 141.7 (m), 141.4 (M), 139.8 (m), 138.1 (M), 136.4 (M), 136.2 (m), 134.2 (M), 134.0 (m), 128.4, 128.4, 128.4, 128.3, 128.3, 128.1, 128.0, 127.9, 127.8, 125.9, 125.8, 69.6 (M), 69.3 (m), 67.7 (m), 67.3 (M), 52.2 (m), 52.1 (M), 39.3 (m), 38.8 (M), 36.3 (M), 36.2 (m), 36.0 (m), 35.8 (M), 31.9 (m), 31.8 (M); IR: 3475, 3029, 2949, 1722, 1655, 1454, 1392, 1337, 1257, 1152, 1058, 915, 770, 747, 697; HRMS: Calculated for $C_{23}H_{27}NO_5Na$ (M+Na+): 420.1787; found: 420.1781.

Methyl (*R)-2-((2*R**,4*S**,6*S**)-6-phenethyl-2-phenyl-2-(trifluoromethyl)-1,3-dioxan-4-yl)-2-(2,2,2-trifluoroacetamido)acetate (7b)**. To a solution of homoallylic alcohol **6** (0.15 mmol, 60 mg) in THF (1.5 mL) at 0°C was added trifluoroacetophenone (0.45 mmol, 0.064 mL) followed by 2.16 M LiHMDS (0.045 mmol, 0.021 mL). The resulting mixture was stirred for 15 min at 0°C. A second portion of trifluoroacetophenone (0.15 mmol, 0.02 mL) and base (0.015 mmol, 0.007 mL) was added, after 15 min a third portion of trifluoroacetophenone (0.15 mmol, 0.02 mL) and base (0.015 mmol, 0.007 mL) was made; then a fourth addition of trifluoroacetophenone (0.15 mmol, 0.02 mL) and base (0.015 mmol, 0.007 mL) was added. The resulting mixture was then stirred at room temperature for 3 h and quenched with a saturated aqueous NH_4Cl solution. The aqueous phase was extracted 3 times with AcOEt and the combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude residue (*syn:anti* 56:44) was then purified by column chromatography using Et_2O/Petroleum ether (9:1) to give the product **7b** as a pale yellow oil (19 mg, 22%). The crude residue (*syn:anti* 56:44) was then purified by column chromatography using Et_2O/Petroleum ether (9:1) to give the product **7b** as a pale yellow oil (19 mg, 22%). The presence of two isomers was observed in the NMR spectra, in a [0.77 (M):0.23 (m)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.81 - 7.89 (m, 15H), 5.14 – 5.32 (m, 2H), 5.03 (d, *J* = 3.3 Hz, 0.78H), 4.74 (d, *J* = 4.5 Hz, 0.22H), 4.58 (dt, *J* = 11.4, 3.3 Hz, 0.77H), 4.42 – 4.46 (m, 0.23 H), 3.87 (M) (s, 2.2H), 3.77 (m) (s, 0.8H), 3.80 – 3.84 (m, 1H), 3.18 (M) (s, 2.2H), 3.15 (m) (s, 0.8H), 2.89 – 2.97 (m, 2H), 2.60 – 2.76 (m, 2H), 1.97– 2.04 (m, 1H), 1.79 – 1.88 (m, 1H), 1.48 – 1.58 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 169.5 (M), 169.2 (m), 158.0 (M), 156.4 (m), 141.5, 136.8 (M), 136.6 (m), 131.8 (m), 131.7 (M), 130.3, 129.3, 129.0, 128.9, 128.9, 128.8, 128.6, 128.5, 128.4, 127.9, 126.3, 121.8 (q, $J_{C\text{-}F}$ = 284.5 Hz), 98.9 (q, $J_{C\text{-}F}$ = 32.0 Hz), 71.4 (M), 70.8 (m), 70.2 (M), 70.1 (m), 68.1 (M), 68.0 (m), 62.3 (m), 61.9 (M), 52.7, 37.4 (M), 37.3 (m), 34.6 (m), 34.1 (M), 33.0 (m), 32.7 (M), 31.3 (m), 30.6 (M); IR: 2952, 2919, 1744, 1699, 1551, 1399, 1308, 1187, 1125, 1062, 998; HRMS: Calculated for $C_{31}H_{32}F_3NO_6Na$ (M+Na^+): 594.2079; Found: 594.2036.

Conflicts of interest

All authors declare that there are no conflicts of interest.

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